Associations between urinary soy isoflavonoids and two inflammatory markers in adults in the United States in 2005-2008

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Abstract: PURPOSE: The aim of this study was to determine the association between urinary isoflavonoid (genistein, daidzein, and the daidzein metabolites O-desmethylangolensin (O-DMA) and equol) excretion and markers of inflammation in adults in the United States in National Health and Nutrition Examination Survey (NHANES) 2005-2008. METHODS: The NHANES is a cross-sectional study conducted by the National Center for Health Statistics to study the health and nutritional status of people living in the United States. The analysis included 1,683 participants from study years 2005-2008 for whom urinary isoflavonoids were measured and who met inclusion criteria. Urinary isoflavonoids were measured by HPLC-APPI-MS/MS. Serum C-reactive protein (CRP) was measured by latex-based nephelometry. White blood cell (WBC) count was measured by Coulter counting. Multivariable linear regression was used to calculate the geometric mean values of the markers, and multivariable logistic regression was used to estimate the odds of high CRP (3 mg/L) and of high WBC count (7,900/ L) by quartile of urinary isoflavonoid (nmol/mg creatinine). RESULTS: The highest quartile of genistein (OR = 0.62; 95 % CI 0.39-0.99) was associated with significantly decreased odds of high CRP compared with the lowest quartile. The sum of daidzein and its metabolites was significantly inversely associated with serum CRP concentration (p-trend = 0.017). Equol was inversely associated with WBC count (p-trend < 0.0001). O-DMA was the only isoflavonoid whose excretion was significantly associated with a decrease in both CRP (p-trend = 0.024) and WBC count (p-trend < 0.0001). CONCLUSIONS: Though no clear pattern emerged, higher excretion of certain soy isoflavonoids was associated with decreased CRP concentration and WBC counts, suggesting a possible inverse association between soy intake and inflammation.

DOI: https://doi.org/10.1007/s10552-013-0198-9

Published in final edited form as:
Cancer Causes Control. 2013 June ; 24(6): 1185–1196. doi:10.1007/s10552-013-0198-9.

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Abstract

Purpose—The aim of this study was to determine the association between urinary isoflavonoid (genistein, daidzein, and the daidzein metabolites *O*-desmethylangolensin (*O*-DMA) and equol) excretion and markers of inflammation in adults in the United States in National Health and Nutrition Examination Survey (NHANES) 2005–2008.

Methods—The NHANES is a cross-sectional study conducted by the National Center for Health Statistics to study the health and nutritional status of people living in the United States. The analysis included 1,683 participants from study years 2005–2008 for whom urinary isoflavonoids were measured and who met inclusion criteria. Urinary isoflavonoids were measured by HPLC-APPI-MS/MS. Serum C-reactive protein (CRP) was measured by latex-based nephelometry. White blood cell (WBC) count was measured by Coulter counting. Multivariable linear regression was used to calculate the geometric mean values of the markers, and multivariable logistic regression was used to estimate the odds of high CRP (≥3 mg/L) and of high WBC count (≥7,900/μL) by quartile of urinary isoflavonoid (nmol/mg creatinine).

Results—The highest quartile of genistein (OR = 0.62; 95 % CI 0.39–0.99) was associated with significantly decreased odds of high CRP compared with the lowest quartile. The sum of daidzein and its metabolites was significantly inversely associated with serum CRP concentration (*p*-trend = 0.017). Equol was inversely associated with WBC count (*p*-trend <0.0001). *O*-DMA was the only isoflavonoid whose excretion was significantly associated with a decrease in both CRP (*p*-trend = 0.024) and WBC count (*p*-trend <0.0001).

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Conflict of interest The authors declare that they have no conflict of interest.

Conclusions—Though no clear pattern emerged, higher excretion of certain soy isoflavonoids was associated with decreased CRP concentration and WBC counts, suggesting a possible inverse association between soy intake and inflammation.

Keywords

Soy isoflavonoids; Inflammation; C-reactive protein; White blood cell count; Cross-sectional studies

Introduction

The World Cancer Research Fund and American Institute for Cancer Research estimate that suboptimal diet, physical activity, and body fatness are responsible for one-third of all cancers [1], and others have estimated that approximately 80 % of colorectal cancers can be attributed to suboptimal diet [2]. Therefore, modification of the diet may be an effective strategy to reduce cancer burden. Individual nutrients or functional foods containing biologically active components can influence cancer-related processes, including inflammation [3]. Inflammation is an important driver of tumor progression and therefore development of cancers, including colorectal cancer. The chronic inflammatory bowel diseases, Crohn's disease, and chronic ulcerative colitis are associated with increased risk of colorectal cancer [4]. Additionally, use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with decreased risk of colorectal cancer and NSAIDs including sulindac and celecoxib reduced the occurrence of recurrent adenomas and reduced the occurrence of colorectal cancer in patients with familial adenomatous polyposis [5–9].

C-reactive protein (CRP), an acute phase response protein, was traditionally used to monitor inflammation in people with chronic inflammatory conditions. More recently, CRP has been recommended as a tool to assess cardiovascular disease risk [10]. Prospective studies and systematic reviews suggest that higher levels of CRP may also be associated with increased risk of colorectal cancer [11–16]. Similarly, elevated white blood cell (WBC) count is a marker of systemic inflammation, and elevated levels are positively correlated with risk of cardiovascular events and various cancers [17, 18]. CRP concentration and WBC count, while components of non-specific systemic responses, can be useful biomarkers because they are easy to measure, they do not have diurnal or seasonal variation, and their levels are not affected by recent meals. However, CRP levels and WBC counts are very responsive to acute infections such as colds and are influenced by smoking, obesity and other chronic disease risk factors [15].

One functional food receiving much attention for its anti-cancer and anti-inflammatory activities is soy. Recent meta-analyses showed that consumption of soy foods was associated with decreased risk of breast cancer, though these associations were stronger in Asian populations than in Western populations. Menopausal status also appeared to be an important effect modifier, as the associations were stronger among postmenopausal women [19, 20]. Soy's anti-cancer and anti-inflammatory activities can be partially attributed to its isoflavonoid content [21]. Soy isoflavonoids are phytoestrogens that can bind to estrogen receptor (ER) α and with even higher affinity to ERβ [22]. Genistein (40–60 %), daidzein (35–50 %), and glycitein (4–12 %) are the major isoflavones in soy and soy products [23]. Daidzein can be metabolized by intestinal bacteria to *O*-desmethylangolensin (*O*-DMA) and equol, both of which are bioavailable and also have estrogenic activities. Approximately 80–90 % of humans have the capability to produce *O*-DMA and 30–50 % can produce equol [24].

While oral estrogen use via hormone replacement therapy in postmenopausal women increases multiple markers of inflammation, including CRP [25], the effects of phytoestrogens such as isoflavonoids on inflammation are not well characterized. Randomized controlled trials to determine any anti-inflammatory activities of soy isoflavonoids in humans have resulted in mixed findings. While a few studies show decreases in some, but not all, inflammation markers studied [26, 27], many show no changes in any inflammatory markers with 6 weeks to 2 years of various soy isoflavonoid interventions [28–35]. The majority of these trials did not control for the soy or isoflavonoid content of the background diets of the participants, and only a few asked the participants to keep food diaries. These studies are also limited in that they supplemented participants' diets with high amounts of partially or completely isolated isoflavonoids and therefore cannot address the effects of biologically relevant amounts of soy isoflavonoids from food sources.

In this study, our aim was to determine the relationship between urinary isoflavonoids and high serum CRP level or WBC count in adults in the United States. We hypothesized that urinary isoflavonoids and the inflammation markers would be inversely related.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional study conducted by the National Center for Health Statistics to study the health and nutritional status of people living in the United States [36]. Our analysis includes data from the 2005–2006 and 2007–2008 NHANES cycles. Because the method for isoflavonoid analysis changed following the 2003–2004 cycle, we limited our analysis to data from 2005 to 2008. The 2005–2006 survey examined a nationally representative sample of 10,348 people, with oversampling of low-income persons, adolescents 12–19 years of age, persons over 60 years of age, Mexican Americans, and African Americans. The 2007–2008 cycle examined 10,149 people with similar oversampling except that all Hispanic persons were oversampled as well. Urinary isoflavonoid concentrations were measured in 2,528 persons 6 years of age and older in 2005–2006 and in 2,424 persons 6 years of age of older in 2007–2008.

We restricted the analysis to participants 18 + years old ($n = 3,428$) to reduce variability in inflammation marker levels. From these, we excluded participants based on other factors that would increase variability of inflammation markers or lead to extreme CRP/WBC values: pregnancy ($n = 129$), current use of female hormones ($n = 184$), poor health status ($n = 108$), or acute infection at the time of the examination, including head or chest colds ($n = 484$), stomach or intestinal illness ($n = 173$), flu, pneumonia, or ear infection ($n = 37$), or whether a doctor or health professional has ever told the participant whether he/she has diabetes ($n = 222$), pre-diabetes ($n = 88$), or kidney disease ($n = 26$). These exclusion criteria were reported by participants during the interview, and pregnancy status was also verified by a laboratory test. Individuals with CRP values that were missing ($n = 106$) or >10 mg/L ($n = 138$) or WBC counts that were missing ($n = 1$), >11,700 ($n = 41$), or <3,000/μL ($n = 8$) were excluded because these extreme values likely reflect acute, and not chronic, inflammation [37, 38]. The final sample size for this study was 1,683 individuals.

Measurements

Blood was collected by venipuncture and spot urine samples were collected at NHANES mobile examination centers (MEC). Samples were processed, stored at −20 °C, and shipped to analytic laboratories. Urinary concentrations of isoflavonoids were measured by HPLC-APPI-MS/MS by the Nutritional Biomarkers Branch, the Division of Laboratory Sciences,

National Center for Environmental Health, Centers for Disease Control and Prevention. Briefly, urine samples were processed using enzymatic deconjugation of the glucuronidated isoflavonoids, and size-exclusion filtration was used. Isoflavonoids were separated by reverse-phase HPLC, detected by APPI-MS/MS, and quantified by isotope dilution. Urinary concentration of creatinine, used to correct urinary levels of analytes for urine dilution, was measured using Beckman Synchron CX3 Clinical Analyzer at the University of Minnesota. CRP was measured by latex-based nephelometry by the Immunology Division, Department of Laboratory Medicine, University of Washington Medical Center. Particles of a polystyrene core and a hydrophilic shell were used to link anti-CRP antibodies covalently. CRP present in test samples formed antigen–antibody complexes with the latex particles, and light scattering was proportional to the concentration of CRP present in the sample. Quality control during sample collection and analysis was monitored by unscheduled visits to collection and laboratory sites. Blind split samples were analyzed and laboratories randomly conducted repeat testing on 2.0 % of all samples. In addition, all quality control methods recommended by manufacturers were followed [36].

We normalized isoflavonoid concentrations to creatinine concentration by dividing values to account for variability between participants in urine dilution [39, 40]. CRP measurements ≥3 mg/L were categorized as “high CRP”; values <3 mg/L were categorized as “low CRP” based on The American Heart Association and Centers for Disease Control and Prevention cutpoint for being at high risk for cardiovascular disease [41]. Further, previous studies on CRP and colorectal cancer have also typically used these cutoff values [11, 13, 14, 42]. Values at or below the CRP limit of detection of 0.2 mg/L were reported as 0.1 mg/L. WBC count was determined using Beckman Coulter MAXM instruments in MECs with the Beckman Coulter method of counting and sizing. Participants with WBC counts ≥7,900/μL (but ≤11,700) were classified as “high WBC count,” and those with values <7,900/μL (but ≥3,000) were classified as “low WBC.” Similar cutpoints were used in previous studies that reported a hazard ratio for lung cancer incidence of 2.81 (95 % CI 1.58–5.01) for those with WBC cell counts ≥8,000/μL compared with those with counts <6,400/μL [17] or an 89 % increase in total cancer mortality comparing those with WBC counts ≥7,400/μL to those with counts ≤5,300/μL [43].

Weight, height, and waist circumference were measured by trained health technicians at MECs. Body mass index (BMI) was calculated as weight in kg divided by squared height in m. Age, sex, alcohol use, smoking habits, physical activity, statin drug use, prescription NSAID use, and household income were self-reported and assessed via interview. Race/ethnicity was also self-reported via interview, and participants were asked to identify as Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or “other race —including multiracial.”

Menopausal status of women was determined using criteria from Kalkwarf et al. [44] adapted to this study, which excludes women taking birth control pills. First, females over 60 were categorized as postmenopausal, and remaining unclassified females with bilateral oophorectomies were also categorized as postmenopausal. Remaining unclassified females who have had a period or pregnancy in the past 12 months or with age <50 years were categorized as premenopausal, and then, remaining unclassified females with age >50 were categorized as postmenopausal.

Statistical analyses

Data were analyzed using survey methods in Stata statistical software version 12.1 (College Station, TX) to account for the complex NHANES sampling design [36]. Data were first explored using descriptive statistics. We then estimated odds ratios (ORs) of high CRP (≥3 mg/L) or high WBC count (≥7,900/μL) by quartiles of normalized isoflavonoid

concentration (nmol or pmol per mg creatinine) using logistic regression and calculated geometric means of CRP concentration and WBC count by isoflavonoid quartile using linear regression. In the demographics-adjusted model, we adjusted for sex, age (continuous), and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/Mexican American, other). In the multivariable model, we further adjusted for BMI (<18.5; 18.5–24.9; 25.0–29.9; ≥30), waist circumference (continuous), alcohol use (average number of drinks/d, indicator variables), menopausal status, physical inactivity (<500 MET-min/week or ≥500 MET-min/week), cigarette smoking status (never, former, or current smoking), and annual household income (increments of $5,000/year, ordinal). These covariates were chosen a priori based on known or suspected confounders of the relationship of isoflavonoids and inflammation. The *p*-trend was obtained by modeling the median value for each quartile of normalized isoflavonoids as a continuous variable.

Results

Table 1 shows the characteristics of the study population overall and by CRP status for the 1,683 participants. The mean age of study participants was 45.3, 45 % were female, and 72 % were non-Hispanic white. The 75th percentile of CRP concentration was 3 mg/L. Compared with those with low CRP, participants with high CRP (≥3 mg/L) were older, were more likely to be non-white, had higher BMI and waist circumference, were less physically active, drank fewer alcoholic drinks per day, and had a lower annual household income. The distribution of smoking status and the proportion of participants using statins or prescription NSAIDS were similar between the two groups. Similar patterns to high versus low CRP were observed when comparing participants with high to low WBC counts (Table 2), except that those with high WBC count drank similar numbers of alcoholic drinks per day ($p = 0.75$), were more likely to be current smokers (40.2 vs. 18.1 %, $p < 0.0001$) or to be self-classified as non-Hispanic white (76.0 vs. 70.9 %, $p = 0.048$), and less likely to be former (18.5 vs. 26.9 %, $p = 0.01$) or never smokers (41.3 vs. 55.0 %, $p = 0.0007$), or to be self-classified as “other” race (3.4 vs. 7.3 %, $p = 0.007$).

Demographics (sex, age, and race/ethnicity)-adjusted and multivariable-adjusted ORs for high versus low CRP by quartile of isoflavonoid excretion are shown in Table 3. Demographics-adjusted ORs for each quartile compared with the lowest quartile showed general trends toward decreased odds of high CRP with higher isoflavonoids, though these results were not statistically significant. Adjustment for NHANES cycle did not alter the findings, and cycle-specific results were similar to the combined findings (data not shown). After further adjustment for menopausal status, waist circumference, BMI, physical activity, alcohol use, smoking status, and household income (multivariable-adjusted model), the highest quartile of genistein was significantly associated with decreased risk of high CRP (OR = 0.62, 95 % CI 0.39–0.99), and the second, third, and fourth quartiles of daidzein were associated with decreased risk of high CRP, though the only statistically significant reduction was observed in the third quartile (OR = 0.59, 95 % CI 0.35–0.98). While no other isoflavonoid was significantly associated with decreased odds of high CRP, genistein, daidzein, the sum of daidzein and its metabolites, and the sum of all four isoflavonoids all showed general trends toward decreased ORs of high CRP for quartiles 2, 3, and 4 versus quartile 1. However, post hoc analyses comparing quartiles 2–4 to quartile 1 for these isoflavonoids did not result in a statistically significant decrease in odds of high CRP (data not shown).

We calculated the geometric mean CRP concentration by quartiles of urinary isoflavonoids using the multivariable-adjusted model (Table 3). The highest quartiles of *O*-DMA and of daidzein + *O*-DMA + equol were significantly inversely associated with serum CRP levels, and significant decreasing trends were observed (*p*-trend = 0.024 and 0.017, respectively).

O-DMA was also associated with significantly decreased geometric mean WBC counts in the third (6,920 cells/μL, p <0.05) and fourth (6,760 cells/μL, p <0.001) quartiles compared with the lowest quartile (7,060 cells/μL) and with an overall decreasing trend (p-trend <0.0001) (Table 4). Equol, while not associated with decreases in CRP levels, was associated with decreased geometric mean WBC counts comparing the highest quartile to the lowest (6,760 vs. 7,020 cells/μL, p <0.0001) and with decreasing WBC count with increasing equol (p-trend <0.0001). The ORs of high WBC count associated with the second, third, or fourth quartiles of *O*-DMA and equol were non-significantly decreased in both the demographics- and multivariable-adjusted models. Genistein, daidzein, the sum of daidzein and its metabolites, or of all four isoflavonoids were not associated with statistically significant changes in WBC count.

Discussion

While we found no overall patterns of associations between urinary isoflavonoids and serum CRP or WBC count, genistein, daidzein, *O*-DMA, and daidzein plus its metabolites were associated with decreasing CRP to varying degrees, while *O*-DMA and equol were associated with decreasing WBC count, suggesting a possible inverse association between certain isoflavonoids and inflammation.

To our knowledge, this is the first observational analysis examining the association between urinary isoflavonoids and inflammation markers. A recent cross-sectional analysis in Chinese women showed that soy intake in the past year was inversely associated with two out of eight inflammatory markers examined and that soy intake in the past 24 h was associated with inverse relationships with five out of eight markers, including interleukin-6, inter-leukin-1β, tumor necrosis factor α (TNFα), and TNFα receptors 1 and 2 [45]. Soy food intake was not inversely associated with CRP levels in this study, and elevated WBC count was not examined. Our findings are consistent with this study because we found that isoflavonoids are not similarly associated with different inflammatory markers. However, our study differs in that we examined individual urinary isoflavonoids, which are more representative of biologically effective doses of isoflavonoids, and not dietary soy intake.

The cutoff values for high versus low CRP and WBC count were chosen based on reports of increased risk of colorectal and other cancers for individuals with similar or higher values [11, 18, 46–48]. A recent meta-analysis showed that a 1-unit increase in ln-transformed CRP concentration is associated with a relative risk of colorectal cancer of 1.12 (95 % CI 1.02, 1.26) [16]. Had we categorized CRP or WBC differently in the present analysis, we might have observed differences in the magnitude of the association with urinary isoflavonoid quartiles.

This study has several strengths for studying the associations of urinary isoflavonoids with markers of inflammation. First, we used NHANES 2005–2008, a nationally representative sample of individuals. In addition, creatinine-normalized urinary isoflavonoid values integrate isoflavonoid intake from all sources, which is challenging to capture via food frequency questionnaires or 24-h recalls, particularly in populations with low soy intake. For example, using NHANES data from 2001 to 2004, Frankenfeld [49] demonstrated that consumption of milk and milk products, but not of legumes, was a significant correlate of urinary equol levels, which likely reflected equol intake from milk. Further, the ubiquity of soy products, particularly hidden soy products, in the diets of adults in the United States can result in inaccurate recall of soy intake. The use of urinary isoflavonoid measurements also captures individuals' ability to process daidzein to equol or *O*-DMA. Another strength of this study is the use of latex-based nephelometry to measure serum CRP in NHANES 2005–

2008. This method has a much lower limit of detection than methods used in previous NHANES surveys.

This study also has some important limitations. First, our analysis, like all cross-sectional analyses, is subject to residual confounding and lack of temporality. Another limitation is the narrow range of isoflavonoid exposure in the US population. Habitual consumption of foods high in isoflavones is rare in this population as whole and is only expected in population subgroups, including Asian Americans. However, NHANES includes Asian American race in the "other" race/ethnicity category, which comprises only 6 % of the population. Therefore, it is difficult to examine the effects of very high isoflavonoid exposure. To address this limitation, we conducted post hoc analyses comparing the highest quartile of isoflavonoid exposure to the sum of quartiles 1–3 or comparing the sum of quartiles 2–4 to the lowest quartile of exposure, but these analyses did not yield any significant results (data not shown).

The excretory half-life of soy isoflavonoids ranges from 3 to 10 h [39]. Because NHANES only collected spot urine samples at one point in time, the urinary isoflavonoid concentrations in our analysis only represent very recent soy intake. However, in two separate studies, one in a middle-aged and older Chinese population in Singapore with high daily soy intake and one in a multi-ethnic population of women, biomarkers in spot urine samples taken on random dates correlated well with overall soy intake [50, 51]. In a randomized, double-blinded, placebo-controlled trial testing effects of supplemental soy protein on 350 postmenopausal women, spot urine isoflavonoid levels displayed high correlation with plasma isoflavonoid levels (between-subject Pearson correlation median $r = 0.80$) [52]. Urinary isoflavonoid levels have also been reported to correlate well with serum isoflavonoid levels in a cross-sectional sample of participants not randomized to consume supplemental soy [39]. These high correlations of plasma and urine isoflavonoid levels suggest that the amounts observed in the urine will approximate the biologically effective doses of these compounds. Future studies should focus on using multiple urinary isoflavonoid measurements over time to investigate the relationship with inflammation.

The plasma half-life of CRP is approximately 19 h [15]. While CRP values are not influenced by recent food intake, CRP is part of a non-specific inflammatory response and its concentration could be influenced by recent infection, surgery, medications, autoimmune diseases, and other acute or chronic conditions. We excluded those with self-reported acute infections, poor health status at the time of examination, or select chronic conditions, but there could still be residual confounding from medications or other conditions.

Most variables included in our final models and for exclusion criteria were reported by participants during the interview, including race/ethnicity, physical activity, smoking status, household income, and current health status and conditions. Inaccurate recall and misclassification are possible with these variables. In addition, NHANES' "other" race/ethnicity category includes Asian Americans, who have higher average soy intake and lower average inflammatory marker levels than those of other race/ethnicity groups in the United States [53–55]. Further, participants were asked to identify with one only one race/ethnicity category, and those who identified with multiple were classified as "other." Because NHANES does not collect more detailed race/ethnicity information, we cannot rule out residual confounding due to incomplete classification.

In conclusion, the results of our study showed that excretion of select isoflavonoids was associated with decreased odds of high inflammatory markers and with decreasing circulating levels of the markers. *O*-DMA was the only isoflavonoid whose excretion was inversely associated with circulating levels of both CRP and WBC count. This cross-

sectional analysis suggests possible inverse associations between soy intake and inflammation, though no clear patterns of associations with individual isoflavonoids emerged. Future prospective cohort studies with multiple measurements of isoflavonoids and inflammatory markers will help to clarify the relationship between soy isoflavonoids and inflammation, which will help to inform whether dietary soy can decrease the risk of cancer and other inflammation-associated diseases.

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Table 1

Characteristics of adults in NHANES 2005–2008 subset for which urinary isoflavonoids were measured, by low and high C-reactive protein (CRP) status

	Unadjusted values				Sex-, age-, and race-adjusted values			
	Low CRP *n* = 1,269	High CRP[a] *n* = 414	*p* value	Total *n* = 1,683	Low CRP *n* = 1,269	High CRP[a] *n* = 414	*p* value	Total
Female[b] (%)	44.1	47.9	0.22	45.0	53.9	52.4	0.60	53.5
Age[c] (year)								
Mean	44.2	49.0	<0.0001	45.3	43.1	48.0	<0.0001	44.3
SE	0.6	0.9		0.5	0.6	0.9		0.5
Race[d] (%)			0.33					
White, not Hispanic	73.7	67.5	0.06	72.3	74.9	66.2	<0.0001	72.9
Black, not Hispanic	9.3	13.0	0.038	10.1	8.9	13.4	0.018	9.9
Hispanic/Mexican American	10.4	14.8	0.024	11.3	9.7	15.7	0.005	11.0
Other	6.7	4.7	0.22	6.2	6.5	4.7	0.27	6.1
Waist circumference (cm)								
Mean	93.1	105.1	<0.0001	95.7	93.0	104.6	<0.0001	95.8
SE	0.6	1.0		0.6	0.5	0.9		0.5
BMI (kg/m^2)			<0.0001				<0.0001	
<18.5	2.7	1.5	0.11	2.4	2.6	1.6	0.20	2.4
18.5–24.9	38.4	14.6	<0.0001	33.2	38.9	15.0	<0.0001	33.4
25.0–29.9	38.0	30.7	0.03	36.5	38.2	30.2	0.017	36.4
≥30.0	20.8	53.2	<0.0001	27.9	20.3	53.2	<0.0001	27.8
Meeting physical activity requirements (%)	49.9	39.0	0.002	47.5	52.5	61.2	0.009	54.6
Alcoholic drinks per day								
Mean	1.0	0.8	0.025	0.9	0.9	0.8	0.024	0.9
SE	0.04	0.05		0.03	0.03	0.05		0.03
Cigarette smoking status (%)			0.27				0.66	
Never	50.2	54.6	0.18	51.2	52.6	56.5	0.24	53.5
Former	25.3	22.0	0.27	24.6	24.7	19.2	0.06	23.5
Current	24.4	23.3	0.67	24.2	22.7	24.3	0.53	23.0
Prescription NSAID use (%)	3.2	3.0	0.89	3.1	3.6	2.8	0.48	3.4
Statin use (%)	11.1	8.9	0.24	10.6	12.0	6.7	0.002	10.8

	Unadjusted values				Sex-, age-, and race-adjusted values			
	Low CRP *n* = 1,269	High CRP[a] *n* = 414	*p* value	Total *n* = 1,683	Low CRP *n* = 1,269	High CRP[a] *n* = 414	*p* value	Total
Annual household income ($1,000)								
Mean	62.3	55.2	0.011	60.7	59.8	54.3	0.045	58.4
SE	1.7	2.5		1.6	1.8	2.6		1.7
CRP (mg/L)								
Mean	1.07	5.16	<0.0001	1.96	1.08	5.14	<0.0001	2.08
SE	0.03	0.10		0.06	0.03	0.10		0.03
WBC count (1,000 cells/μL)								
Mean	6.82	7.35	<0.0001	6.94	6.77	7.36	<0.0001	6.91
SE	0.08	0.10		0.07	0.07	0.10		0.06
Genistein (nmol/mg creatinine)								
Mean	1.67	1.18	0.10	1.57	1.85	1.24	0.058	1.72
SE	0.23	0.19		0.18	0.28	0.20		0.23
Daidzein (nmol/mg creatinine)								
Mean	3.95	3.41	0.57	3.83	4.22	3.47	0.42	4.05
SE	0.49	0.78		0.42	0.54	0.77		0.46
O-DMA (pmol/mg creatinine)								
Mean	0.97	1.06	0.84	0.99	1.02	1.07	0.92	1.03
SE	0.20	0.39		0.17	0.23	0.40		0.20
Equol (pmol/mg creatinine)								
Mean	1.06	0.22	0.0005	0.88	0.96	0.13	<0.0001	0.77
SE	0.23	0.05		0.19	0.21	0.06		0.16
Daidzein + *O*-DMA + equol (nmol/mg creatinine)								
Mean	5.98	4.69	0.33	5.69	6.21	4.66	0.25	5.85
SE	0.79	1.06		0.66	0.81	1.07		0.67
Genistein + daidzein + *O*-DMA + equol (nmol/mg creatinine)								
Mean	7.65	5.87	0.26	7.26	8.06	5.91	0.18	7.57
SE	0.99	1.23		0.81	1.04	1.23		0.86

[a]High CRP is defined as serum CRP ≥3 mg/L

[b]Adjusted values were adjusted for age and race/ethnicity only

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[c] Adjusted values were adjusted for sex and race/ethnicity only

[d] Adjusted values were adjusted for sex and age only

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Table 2

Characteristics of adults in NHANES 2005–2008 subset for which urinary isoflavonoids were measured, by low and high white blood cell (WBC) count status

	Unadjusted values				Sex-, age-, and race-adjusted values			
	Low WBC *n* = 1,269	High WBC[a] *n* = 414	*p* value	Total *n* = 1,683	Low WBC *n* = 1,269	High WBC[a] *n* = 414	*p* value	Total
Female[b] (%)	46.7	40.3	0.08	45.0	47.8	42.7	0.16	53.5
Age[c] (year)								
Mean	46.0	43.3	0.005	45.3	44.9	42.2	0.005	44.3
SE	0.6	0.7		0.5	0.6	0.7		0.5
Race[d] (%)			0.10				0.04	
White, not Hispanic	70.9	76.0	0.048	72.3	71.2	77.4	0.014	72.9
Black, not Hispanic	11.4	6.7	<0.0001	10.1	11.3	6.2	<0.0001	9.9
Hispanic/Mexican American	10.4	13.9	0.041	11.3	10.3	13.1	0.09	11.0
Other	7.3	3.4	0.007	6.2	7.2	3.2	0.004	6.1
Waist circumference (cm)								
Mean	94.5	98.8	0.002	95.7	94.5	98.7	0.002	95.8
SE	0.8	0.9		0.6	0.6	0.9		0.5
BMI (kg/m^2)			0.01				0.015	
<18.5	2.6	2.0	0.48	2.4	2.5	1.8	0.44	2.4
18.5–24.9	35.8	26.4	0.02	33.2	35.7	27.0	0.029	33.4
25.0–29.9	36.3	36.9	0.84	36.5	36.3	36.7	0.914	36.4
≥30.0	25.4	34.6	0.01	27.9	25.5	34.5	0.013	27.8
Meeting physical activity requirements (%)	49.1	43.2	0.1	47.5	47.6	39.9	0.07	54.6
Alcoholic drinks per day								
Mean	0.9	0.9	0.75	0.9	0.9	0.9	0.64	0.9
SE	0.04	0.04		0.03	0.03	0.04		0.03
Cigarette smoking status (%)			<0.0001				<0.0001	
Never	55.0	41.3	0.007	51.2	56.7	44.3	0.001	53.5
Former	26.9	18.5	0.01	24.6	25.5	17.7	0.029	23.5
Current	18.1	40.2	<0.0001	24.2	17.7	38.0	<0.0001	23.0
Prescription NSAID use (%)	3.1	3.3	0.87	3.1	3.2	3.9	0.60	3.4

	Unadjusted values				Sex-, age-, and race-adjusted values			
	Low WBC *n* = 1,269	**High WBC[a] *n* = 414**	***p* value**	**Total *n* = 1,683**	**Low WBC *n* = 1,269**	**High WBC[a] *n* = 414**	***p* value**	**Total**
Statin use (%)	11.4	8.5	0.10	10.6	11.2	9.8	0.47	10.8
Annual household income ($1,000)								
Mean	62.2	56.8	0.018	60.7	60.3	53.4	0.002	58.4
SE	1.7	2.2		1.6	1.8	2.3		1.7
CRP (mg/L)								
Mean	1.84	2.30	0.001	1.96	1.87	2.39	<0.001	2.08
SE	0.07	0.12		0.06	0.06	0.11		0.03
WBC count (1,000 cells/μL)								
Mean	6.10	9.15	<0.0001	6.94	6.10	9.15	<0.0001	6.91
SE	0.05	0.07		0.07	0.05	0.07		0.06
Genistein (nmol/mg creatinine)								
Mean	1.67	1.30	0.30	1.57	1.78	1.53	0.45	1.72
SE	0.24	0.24		0.18	0.28	0.25		0.23
Daidzein (nmol/mg creatinine)								
Mean	4.01	3.35	0.58	3.83	4.17	3.73	0.73	4.05
SE	0.062	0.84		0.42	0.64	0.88		0.46
O-DMA (pmol/mg creatinine)								
Mean	1.01	0.93	0.79	0.99	1.04	1.02	0.95	1.03
SE	0.20	0.27		0.17	0.22	0.31		0.20
Equol (pmol/mg creatinine)								
Mean	0.85	0.95	0.86	0.88	0.74	0.85	0.85	0.77
SE	0.23	0.45		0.19	0.21	0.47		0.16
Daidzein + *O*-DMA + equol (nmol/mg creatinine)								
Mean	5.87	5.22	0.71	5.69	5.95	5.59	0.85	5.85
SE	0.90	1.27		0.66	0.90	1.35		0.67
Genistein + daidzein + *O*-DMA + equol (nmol/mg creatinine)								
Mean	7.54	6.53	0.62	7.26	7.73	7.11	0.77	7.57
SE	1.11	1.47		0.81	1.13	1.56		0.86

[a] High WBC is defined as WBC counts ≥7,900/μL

[b] Adjusted values were adjusted for age and race/ethnicity only

[c] Adjusted values were adjusted for sex and race/ethnicity only

[d] Adjusted values were adjusted for sex and age only

Table 3

Odds ratios of high CRP[a] and geometric mean serum CRP concentrations by quartiles of urinary isoflavonoids in adults in NHANES 2005–2008

Isoflavonoid	Q1	Q2	Q3	Q4	*p* for trend
Genistein					
Range (nmol/mg creatinine)	B0.030	0.031–0.080	0.081–0.259	≥0.260	
Demographics-adjusted OR (95 % CI)[b]	Ref	0.72 (0.43, 1.21)	0.85 (0.50, 1.44)	0.69 (0.45, 1.06)	0.23
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.61 (0.34, 1.10)	0.74 (0.42, 1.32)	0.62 (0.39, 0.99)*	0.13
Geometric mean CRP [mg/L (95 % CI)][c]	2.06 (1.94, 2.18)	1.76 (1.66, 1.86)**	2.03 (1.89, 2.18)	1.91 (1.76, 2.07)	0.24
Daidzein					
Range (nmol/mg creatinine)	B0.068	0.069–0.194	0.195–0.658	≥0.659	
Demographics-adjusted OR (95 % CI)[b]	Ref	0.93 (0.65, 1.35)	0.69 (0.45, 1.07)	0.87 (0.57, 1.34)	0.33
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.79 (0.48, 1.31)	0.59 (0.35, 0.98)	0.77 (0.51, 1.18)	0.19
Geometric mean CRP [mg/L (95 % CI)][c]	1.95 (1.82, 2.08)	1.98 (1.86, 2.11)	1.86 (1.74, 1.98)	1.98 (1.81, 2.15)	0.75
O-DMA					
Range (pmol/mg creatinine)	B2.616	2.617–12.184	12.185–70.543	≥70.544	
Demographics-adjusted OR (95 % CI)[b]	Ref	0.95 (0.65, 1.38)	1.01 (0.64, 1.59)	0.67 (0.42, 1.06)	0.12
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.98 (0.66, 1.46)	1.01 (0.60, 1.70)	0.78 (0.45, 1.34)	0.36
Geometric mean CRP [mg/L (95 % CI)][c]	1.93 (1.78, 2.08)	2.11 (2.00, 2.23)	2.01 (1.88, 2.14)	1.74 (1.62, 1.87)*	0.024
Equol					
Range (pmol/mg creatinine)	B11.850	11.851–25.318	25.319–52.737	≥52.738	
Demographics-adjusted OR (95 % CI)[b]	Ref	1.30 (0.89, 1.90)	0.94 (0.59, 1.51)	0.92 (0.57, 1.49)	0.43
Multivariable-adjusted OR (95 % CI)[c]	Ref	1.23 (0.80, 1.88)	0.89 (0.56, 1.41)	0.90 (0.53, 1.54)	0.43
Geometric mean CRP [mg/L (95 % CI)][c]	1.90 (1.77, 2.03)	2.09 (1.95, 2.23)	1.91 (1.77, 2.06)	1.90 (1.78, 2.01)	0.37
Daidzein + *O*-DMA + equol					
Range (nmol/mg creatinine)	B0.082	0.083–0.232	0.233–0.782	≥0.783	
Demographics-adjusted OR (95 % CI)[b]	Ref	0.73 (0.46, 1.16)	0.67 (0.43, 1.05)	0.62 (0.40, 0.98)	0.053
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.72 (0.42, 1.23)	0.66 (0.39, 1.12)	0.62 (0.37, 1.05)	0.096
Geometric mean CRP [mg/L (95 % CI)][c]	2.01 (1.87, 2.14)	1.97 (1.88, 2.07)	2.04 (1.90, 2.18)	1.79 (1.64, 1.94)*	0.017
Genistein + daidzein + *O*-DMA + equol					

Isoflavonoid	Q1	Q2	Q3	Q4	*p* for trend
Range, nmol/mg creatinine					
Demographics-adjusted OR (95 % CI)[b]	Ref	0.92 (0.61, 1.38)	0.70 (0.43, 1.15)	0.76 (0.49, 1.19)	0.15
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.78 (0.46, 1.31)	0.61 (0.35, 1.07)	0.71 (0.45, 1.12)	0.13
Geometric mean WBC count (1,000 cells/μL)[c]	1.94 (1.82, 2.07)	2.03 (1.92, 2.14)	1.91 (1.78, 2.04)	1.90 (1.75, 2.06)	0.14

* p <0.05 compared to Q1;

** p <0.001 compared to Q1

[a] High CRP is defined as serum CRP ≥3 mg/L

[b] Adjusted for age, sex, and race/ethnicity

[c] Adjusted for age, sex, race/ethnicity, BMI, waist circumference, menopausal status, physical activity, alcohol intake, smoking status, and household income

Table 4

Odds ratios of high WBC count[a] and geometric mean WBC count by quartiles of urinary isoflavonoids in adults in NHANES 2005–2008

Isoflavonoid	Q1	Q2	Q3	Q4	*p* for trend
Genistein					
Range (nmol/mg creatinine)	≤0.030	0.031–0.080	0.081–0.259	≥0.260	
Demographics-adjusted OR (95 % CI)[b]	Ref	1.28 (0.83, 1.97)	1.18 (0.79, 1.76)	1.16 (0.78, 1.71)	0.56
Multivariable-adjusted OR (95 % CI)[c]	Ref	1.22 (0.74, 2.02)	1.13 (0.76, 1.67)	1.19 (0.82, 1.74)	0.41
Geometric mean WBC count (1,000 cells/μL)[c]	6.87 (6.78, 6.96)	6.97 (6.90, 7.05) *	6.97 (6.85, 7.09)	6.88 (6.75, 7.01)	0.07
Daidzein					
Range (nmol/mg creatinine)	≤0.068	0.069–0.194	0.195–0.658	≥0.659	
Demographics-adjusted OR (95 % CI)[b]	Ref	2.01 (1.26, 3.22)	1.43 (0.93, 2.20)	1.25 (0.86, 1.82)	0.76
Multivariable-adjusted OR (95 % CI)[c]	Ref	2.12 (1.29, 3.50)	1.51 (0.95, 2.40)	1.29 (0.88, 1.87)	0.66
Geometric mean WBC count (1,000 cells/μL)[c]	6.77 (6.67, 6.87)	7.17 (7.06, 7.27) **	6.95 (6.87, 7.04) *	6.80 (6.67, 6.93)	0.77
O-DMA					
Range, pmol/mg creatinine	≤2.616	2.617–12.184	12.185–70.543	≥70.544	
Demographics-adjusted OR (95 % CI)[b]	Ref	1.00 (0.71, 1.40)	0.90 (0.64, 1.27)	0.71 (0.48, 1.05)	0.07
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.98 (0.66, 1.47)	0.94 (0.62, 1.43)	0.82 (0.51, 1.33)	0.40
Geometric mean WBC count (1,000 cells/μL)[c]	7.06 (6.96, 7.16)	7.00 (6.90, 7.09)	6.92 (6.81, 7.02) *	6.76 (6.65, 6.87) **	<0.0001
Equol					
Range (pmol/mg creatinine)	≤1.850	11.851–25.318	25.319–52.737	≥52.738	
Demographics-adjusted OR (95 % CI)[b]	Ref	0.90 (0.63, 1.28)	0.93 (0.60, 1.43)	0.69 (0.44, 1.11)	0.14
Multivariable-adjusted OR (95 % CI)[c]	Ref	0.83 (0.58, 1.19)	0.89 (0.53, 1.50)	0.74 (0.43, 1.28)	0.35
Geometric mean WBC count (1,000 cells/μL)[c]	7.02 (6.91, 7.14)	6.93 (6.83, 7.04)	7.02 (6.91, 7.13)	6.76 (6.67, 6.85) ***	<0.0001
Daidzein + *O*-DMA + equol					
Range (nmol/mg creatinine)	≤0.082	0.083–0.232	0.233–0.782	≥0.783	
Demographics-adjusted OR (95 % CI)[b]	Ref	1.64 (1.03, 2.62)	1.14 (0.76, 1.73)	1.15 (0.77, 1.72)	0.86
Multivariable-adjusted OR (95 % CI)[c]	Ref	1.85 (1.13, 3.04)	1.19 (0.78, 1.82)	1.27 (0.81, 1.98)	0.94
Geometric mean WBC count (1,000 cells/μL)[c]	6.93 (6.81, 7.05)	7.05 (6.97, 7.14)	6.86 (6.78, 6.95)	6.85 (6.73, 6.97)	0.12
Genistein + daidzein + *O*-DMA + equol					

Isoflavonoid	Q1	Q2	Q3	Q4	*p* for trend
Range (nmol/mg)creatinine	≤0.400	0.401–0.956	0.957–3.074	≥3.075	
Demographics-adjusted OR (95 % CI)[b]	Ref	1.33 (0.84, 2.12)	1.23 (0.76, 2.00)	1.10 (0.74, 1.62)	0.82
Multivariable-adjusted OR (95 % CI)[c]	Ref	1.42 (0.85, 2.37)	1.30 (0.79, 2.13)	1.16 (0.74, 1.81)	0.67
Geometric mean WBC count (1,000 cells/μL)[c]	6.91 (6.80, 7.02)	6.96 (6.88, 7.04)	7.02 (6.93, 7.11)	6.81 (6.68, 6.93)	0.57

[*] $p < 0.05$ compared to Q1;

[**] $p < 0.001$ compared to Q1;

[***] $p < 0.0001$ compared to Q1

[a] High WBC count is defined as white blood cell counts ≥7,900/μL

[b] Adjusted for age, sex, and race/ethnicity

[c] Adjusted for age, sex, race/ethnicity, BMI, waist circumference, menopausal status, physical activity, alcohol intake, smoking status, and household income